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Full Length Article

A COVID-19 Primer for Pediatric Primary Care Providers

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Abstract

COVID-19 has challenged pediatric primary care practitioners to rapidly learn new information and adapt clinical practice in response to the continuous evolution of prevention, diagnosis, and management measures. The introduction of COVID-19 vaccination for age-eligible pediatric populations has afforded increased opportunities for disease prevention, and the pandemic has highlighted the need for pediatricians to serve as advocates for their patients and for their communities.

Introduction

COVID-19 has affected, and continues to impact, nearly every aspect of healthcare for children and adolescents. The pandemic has necessitated pediatrician familiarity with nuanced topics including infection prevention and control, epidemiology, laboratory diagnostics (molecular and otherwise), and vaccinology. COVID-19 has also exemplified the importance of

pediatricians' advocacy for patients as individuals and within the larger context of public health. This review elaborates on the aspects of COVID-19 prevention, diagnosis, outpatient management, and advocacy most relevant to pediatric and adolescent providers in primary care settings. Neither inpatient management strategies nor sequelae of pediatric COVID-19 infection such as MIS-C are discussed within this review.

Background

Coronaviruses are enveloped, single-stranded RNA viruses. Prior to the discovery of SARS-CoV-2 (the virus which causes COVID-19), six coronavirus species were known to cause infections in humans. Among these species, HCoV-229E, HCoV-NL63, HCoV-OC43, and HCoV-HKU1 are endemic and are primarily known for causing mild-to-moderate respiratory illness. As with SARS-CoV-2, bats are suspected of being a primary ancestral source of the other two species (SARS-CoV and MERS-CoV).[1-3]

SARS-CoV-2 has been evolving since the beginning of the pandemic. Variants of the original virus have emerged due to genetic mutations, some of which have allowed for enhanced transmissibility and infectivity. SARS-CoV-2 variants are classified by the Pango nomenclature system (which assigns a series of letters, numbers, and dots to denote variant ancestry according to viral genome sequencing characteristics) and by the World Health Organization (WHO) method that uses letters of the Greek alphabet.[4-6] The WHO classification terminology is more frequently used by the lay public. For example, the variant denoted B.1.1.529 according to the Pango system is more widely known by its WHO moniker - the Omicron variant.

The U.S. SARS-CoV-2 Interagency Group further categorizes variants by their circulation at national and regional levels and by the impact of mutations on disease severity, transmissibility, and effectiveness of medical countermeasures.[4] Within this schema, there are

two categories most relevant to healthcare providers. *Variants of Concern* actively demonstrate increased transmissibility, more severe disease, reduced neutralization by antibodies from a prior infection or vaccination, and/or failure to be detected by current diagnostic testing. *Variants of High Consequence* also possess such features, while current prevention measures and treatment options against variants in this category are significantly reduced.

Epidemiology

The primary mode of transmission of SARS-CoV-2 is through exposure to the respiratory secretions of an infected person, either directly via respiratory droplets or through inhalation of infectious aerosols.[7] The durability of the virus on fomites and surfaces is unknown but is thought to be relatively brief and influenced by factors including heat, humidity, and surface porousness.[8] The average incubation period of SARS-CoV-2 is 3-5 days (with a range of 2-14 days), with variability noted amongst variants.[9] Viral load and presumed infectiousness peaks early in the course of illness, and infected individuals without immunocompromise are presumed to no longer be infectious after 10 days since symptom onset.[10] Though the infectious dose of SARS-CoV-2 is still unknown, some individuals are known to shed greater quantities of infectious material and may serve as "super spreaders" to others. In adults, there is a correlation between viral load at onset of symptoms and the severity of symptoms of COVID-19.[11] Children have been found to have similar viral loads compared to adults and are known to be efficient spreaders of SARS-CoV-2.[12]

The Delta variant is concerning, as it is estimated to be twice as infectious as previously circulating variants, with higher viral loads among both children and adults relative to previously circulating variants.[13] More recently, the Omicron variant has been estimated to be 2 to 3 times as transmissible as Delta.[14] Despite the evolution of multiple variants, mitigation measures such

as physical distancing of 6 feet or more, universal use of well-fitted face masks, and adequate ventilation have remained the same and have been shown to effectively reduce the likelihood of transmission.[15]

Early in the COVID-19 pandemic, the incidence of SARS-CoV-2 infection among children and adolescents was estimated to be lower than among adults. The true incidence of pediatric COVID-19 was likely unascertainable at that time, given underdiagnosis and underreporting due to a high proportion of asymptomatic and mildly symptomatic infections in children.[16] The widespread closure of schools and childcare settings likely presented fewer opportunities for exposure and thus may have mitigated pediatric cases during that time period.[17] Seroprevalence studies have found that infection rates of SARS-CoV-2 among children are much higher than reported cases of COVID-19 and may be similar to those of adults.[18,19]

Coincident with Delta's emergence as the predominant SARS-CoV-2 variant circulating in the U.S. during the latter half of 2021, children have comprised an increasing proportion of reported cases of COVID-19.[20] This observed increase in the proportion of pediatric cases is likely due to the reduced risk of disease among fully vaccinated adults,[21] as well as increased virus transmission and detection among children. Transmission in schools is strongly influenced by disease incidence in the community, though clusters and outbreaks do occur in schools, camps, and sports settings - particularly when mitigation measures are not fully or consistently implemented.[22-26]

Symptomatology

The list of potential clinical manifestations of COVID-19 disease is extensive. Symptoms can include (but are not limited to) fever, chills, cough, dyspnea, fatigue, diffuse myalgias, headaches, anosmia, ageusia, pharyngitis, rhinorrhea, nasal congestion, nausea, emesis and

diarrhea (https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html). In the pediatric population there exists considerable overlap between the presenting symptoms of COVID-19 and those of numerous common viral illnesses of childhood, including influenza, parainfluenza, respiratory syncytial virus (RSV), and human metapneumovirus. As with influenza, gastrointestinal symptoms can be primary manifestations of COVID-19 in younger children.[27] Parainfluenza and influenza are known to cause croup in young children. In contrast, croup has not been recognized as a presenting clinical manifestation of pediatric COVID-19 infection beyond a small number of cases reported in the medical literature.[28-30] Respiratory syncytial virus (RSV) is the most widely recognized cause of viral bronchiolitis in infants and young children, though parainfluenza and human metapneumovirus also cause bronchiolitis in these age groups.[27] Though bronchiolitis is not one of the most frequently reported signs of pediatric COVID-19 infection, it has been reported as a manifestation in 0.5% - 9.7% of all pediatric COVID-19 cases (with rates as high as 14% observed in hospitalized children).[31]

Much attention has been given to anecdotal reports suggesting that symptoms seen in children infected with the Delta variant differ from those of preceding variants. With the possible exceptions of anosmia and ageusia, which were noted to be relatively common presenting symptoms in children with mild illness during earlier waves of the pandemic when Delta was not yet widely circulating,[32] reported symptoms of children infected with the Delta variant (including fever, cough, headache, and pharyngitis) have been similar to those of earlier variants.[26,32-34]

Clinical diagnosis of pediatric COVID-19 is further confounded by an elevated incidence of mildly symptomatic disease and asymptomatic infections in children.[16,33,35-37] Given this, and given the similarities between clinical manifestations of COVID-19 and those of several other

frequently encountered childhood viral illnesses, extremely high rates of laboratory diagnostic testing for pediatric COVID-19 should be anticipated.

Diagnosis

Children with symptoms of COVID-19 should be tested regardless of age. Testing should be guided not only by symptomatology, but also by the prevalence of disease in the local community.[38] Coinfection with SARS-CoV-2 and other illnesses is possible, and thus ruling in an infection such as influenza or RSV by a positive laboratory test result does not necessarily preclude a concurrent diagnosis of COVID-19.

Diagnostic Testing for SARS-CoV-2

One of the major challenges pediatricians have faced regarding testing in the outpatient setting has been determining the optimal use of nucleic acid amplification tests (NAATs) and rapid antigen tests when assessing for COVID-19. Understanding both population and individual use case scenarios is important and can help inform guidance given to families. NAATs detect specific sequences unique to the RNA genetic material of SARS-CoV-2. NAAT positivity denotes a current infection or a recent infection but, due to prolonged shedding of viral RNA, is not necessarily indicative of viable virus or infectiousness. NAATs for SARS-CoV-2 have high diagnostic sensitivity and specificity but remain more expensive and have highly variable times to results (ranging from minutes to days).[39] Antigen tests detect proteins of the SARS-CoV-2 virus, and generally have lower diagnostic sensitivities than most NAATs. Due to these diagnostic sensitivity discrepancies, confirmation of a negative antigen test result via use of a NAAT is advised for patients who have a high pre-test probability for COVID-19. Antigen tests are generally less expensive than NAATs and have a more rapid turnaround time to results, making them effective in quickly identifying potentially infectious people. Serial antigen testing

may be useful in aiding surveillance efforts.[40] Commercially available antigen tests are also available over-the-counter for at-home use, and these tests generally have similar performance as office-based antigen tests. Regardless of the testing modality utilized, shared decision making between providers and families remains essential and necessitates informed discussions regarding testing modalities, testing limitations, and potential implications of testing results.

Coinfections and Diagnostic Testing

Prior to the onset of the pandemic, the rates of pediatric coinfection with > 1 respiratory viral illness were estimated to range between 10% - 30% (or greater), depending upon the NAAT technique utilized and the specific combinations of viruses for which children are tested simultaneously.[41] However, to date the incidence of pediatric SARS-CoV-2 coinfection with other respiratory viruses (as per studies originating in the U.S., Europe and the Middle East) has been appreciably lower, ranging from 0% - 12%.[34,42-44] As with the incidence of pediatric COVID-19 infections during the early stages of the pandemic, the results of these studies (for which the large majority of data collection occurred during 2020) were invariably affected by factors including mitigation strategies (i.e., stay-at-home/lockdown orders, school closures, masking requirements, etc.) and the viral variants in widespread circulation during the respective study periods.

Despite the relatively low reported incidence of pediatric coinfections, and despite a reported incidence of 3% - 21% in adults,[43,45] multiple molecular diagnostic tests have been developed and subsequently granted emergency use authorization (EUA) by the U.S. Food and Drug Administration (FDA) for concurrent detection of SARS-CoV-2 and additional viruses.[46] These panel NAATs can greatly assist pediatric providers in differentiating between various viral respiratory infections with similar clinical presentations, and can be especially valuable for

circumstances when an accurate viral diagnosis would influence treatment decisions. However, careful consideration is warranted prior to ordering NAATs for detection of SARS-CoV-2 and other coinfecting respiratory viruses because of the oft limited availability of reagents needed to perform these assays and the costs to patients, families, and the healthcare system.

SARS-CoV-2 Antibody Testing

Immunity to SARS-CoV-2 is a complex concept, and interpretation of antibody testing for SARS-CoV-2 is not straightforward. Currently available FDA-authorized assays detect the presence of antibodies to either the SARS-CoV-2 spike or nucleocapsid protein antigens. The nucleocapsid protein is a structure common to all coronaviruses which binds and encircles the single-stranded RNA core of the virus.[47] Antibodies directed against the spike protein of SARS-CoV-2 can develop as a response to either natural infection or vaccination, while anti-nucleocapsid antibodies are generated only by natural infection.[48]

The presence of IgG antibodies to the spike or nucleocapsid proteins of SARS-CoV-2 is not necessarily indicative of protection from future infection or reinfection. This is due to two primary reasons. First, there is not yet an established immune correlate of protection for SARS-CoV-2 (for example, a specific numeric antibody level threshold indicative of protective immunity). However, this is an ongoing area of research. Essentially all serologic testing platforms granted authorization by the FDA to date are either qualitative (for which the reported test result is either ‘positive’ or ‘negative’) or semi-qualitative (the reported test result is either ‘positive’ or ‘negative’ and is accompanied by a numeric value/level).[49] Second, the presence of antibodies against SARS-CoV-2 does not necessarily imply that those antibodies are functionally capable of neutralizing the virus upon exposure. Ascertaining the neutralizing ability of these antibodies requires the use of neutralizing antibody detection testing, and such testing is not

currently available for widespread commercial use. For these reasons, presently available SARS-CoV-2 antibody testing should not be used to determine protection from infection following either natural infection or vaccination. Additionally, antibody testing should not be used to determine the presence of an active infection, as measurable antibody concentrations typically do not begin to develop until 7-14 days after the onset of illness.[48]

Despite the limitations of antibody testing, there are nevertheless circumstances for which antibody testing may be beneficial. Seroconversion of individuals with an initial negative antibody test followed by a subsequent positive antibody test might indicate that an interim illness was due to SARS-CoV-2.[48] A positive antibody test result can be used to support diagnoses complicating a recent COVID-19 infection such as MIS-C or post-acute sequelae of COVID-19 (colloquially known as 'long COVID').

Management

Office-based Management

Most children with COVID-19 can be safely and effectively managed in the outpatient setting. Those with mild symptoms should receive traditional supportive care measures, including treatment of fever with antipyretics and oral hydration to maintain fluid status. Active monitoring of respiratory status is also important. Families with ill children should be counseled on how to properly address signs of disease progression or clinical worsening. Close communication with the pediatric provider is essential, as many families will require assistance with understanding the appropriate isolation guidance to follow to prevent transmission to others.

Guidance throughout much of the pandemic has had pediatric providers explaining to families of ill children that isolation for a full ten days following symptom onset (or alternatively for a full ten days beginning from the date of positive testing if the child is asymptomatic) is

necessary. More recently, updated guidance from the CDC has shortened the duration of isolation to five days if symptoms are resolved or improving and if the individual can continue to wear a proper fitting mask for an additional five days, given increasing evidence that the majority of transmission tends to occur 1-2 days prior to symptom onset and during the first few days of illness.[50] As the prospect of having an ill child isolate at home for 5 to 10 days may seem daunting to families, a thoughtful explanation of the rationale underlying this recommendation (namely, that those infected are able to transmit the virus to others for up to 10 days after symptom onset) is warranted. Providers should inform families that infected children should also be afebrile for at least 24 hours without use of antipyretics and exhibit symptom improvement prior to ending isolation.[51]

Proper office-based evaluation of children with COVID-19 experiencing progression of their symptoms or exhibiting potential signs of impending clinical decompensation is recommended. Such signs and symptoms could include worsening respiratory distress, wheezing, chest pain, decreased urine output, and worsening fatigue bordering on lethargy.[52] The use of pulse oximetry, respiratory rate, hydration status, and rate of progression of these symptoms should be promptly assessed in primary care, with escalation to higher levels of care for those with progressive clinical worsening.

Additionally, providing timely guidance is imperative for those pediatric patients with underlying medical conditions which place them at the highest risk for severe COVID-19 disease. As with adults, children with conditions including obesity, diabetes, chronic lung disease, sickle cell disease and immunosuppression are at increased risk for severe illness. Children with medical complexity (including those with genetic, neurologic or metabolic conditions) and those with congenital heart disease may also be at increased risk for severe

COVID-19 disease.[53] In one study of over 40,000 children and adolescents diagnosed with COVID-19, the relative risk of hospitalization from COVID-19 for those with type 1 diabetes mellitus, obesity, cardiac disorders, neurodevelopmental disorders, essential hypertension and asthma was 2.9 – 7.8 times greater (depending on the respective condition) than for individuals without such conditions.[54] The American Academy of Pediatrics (AAP) has proposed a multi-layered approach for outpatient management of children and youth with special health care needs during the pandemic.[55] This approach encourages the use of telehealth assessments and home-based laboratory drawing services whenever reasonably feasible, mitigation strategies to reduce the risk of infection, and ongoing multidisciplinary engagement amongst patients, caregivers, and the medical home.

With the coincident onset of the COVID-19 pandemic and the rapid expansion of telemedicine, the use of telehealth in primary care pediatrics has indeed afforded providers with additional abilities to monitor patients with COVID-19 disease.[56] Telehealth provides opportunities for primary care pediatricians to maintain regular contact with patients, address both acute illness and chronic conditions, and to ensure pediatric patients are cared for at appropriate levels of care.[57]

Anti-SARS-CoV-2 Monoclonal Antibodies

Outpatient therapies for management of COVID-19 infection are currently limited but are gradually increasing in availability for children and adolescents. Monoclonal antibody therapies (mAbs) with neutralizing activity against SARS-CoV-2 now have FDA EUA for treatment of mild-to-moderate disease for certain high risk pediatric patients (including newborns) and for use as post-exposure prophylaxis in these populations (Table 1), though these mAbs may be in short supply and may have reduced performance against certain variants of SARS-CoV-2.[58-60] When

used as post-exposure prophylaxis, eligible individuals receiving mAbs should be unimmunized, incompletely immunized, or fully vaccinated but not expected to mount an adequate immune response to a complete vaccination series (eg, immunocompromised).

Though small numbers of pediatric and adolescent participants were included in the BLAZE-1 trial (which evaluated the safety and efficacy of the mAb cocktail bamlanivimab and etesevimab),[60,61] and even though phase III of the casirivimab and imdevimab trial assessing efficacy in those 12-17 years of age is currently ongoing,[62,63] the impetus for closely studying these drugs in the pediatric population has been low because of the overall greater risk of severe COVID-19 disease in the adult population.[64] Whether the increased frequencies of pediatric hospitalizations and severe illness in children resulting from Delta or future variants spur greater investigation into more widespread use of these agents for children and adolescents remains to be seen. Until such time, decisions regarding when eligible pediatric patients should receive mAbs will be primarily based on the discretion of the treating clinician.

Vaccines and Vaccination

Following the swift global dissemination of SARS-CoV-2, development of a vaccine became a high priority to restrain the spread of COVID-19 and reduce morbidity and mortality. Intense investigation and vaccine development occurred with sustained commitment from researchers, the pharmaceutical industry, and many governments worldwide. Collaborative efforts have been essential to ensure rapid large-scale production and delivery of vaccines to billions of people throughout the world.

Several different vaccines continue to be developed utilizing a variety of strategies. Pre-clinical, phase I, and phase II through phase III studies (as well as some phase IV interventional studies) are being carried out concurrently, with reporting on safety, immunogenicity and

efficacy data of these various vaccine candidates.[65] The mRNA-based COVID-19 vaccines include the mRNA1273/Moderna vaccine and the BNT162b2/Pfizer-BioNTech vaccine. The latter is the only vaccine currently with FDA authorization for use in children 5 years of age and older. The only other vaccine currently with FDA authorization for use in the U.S. (though not for individuals < 18 years) is the DNA-based non-replicating live adenovirus vector vaccine Ad26.COV2.S produced by Janssen Pharmaceuticals-Johnson & Johnson.

Vaccine Mechanisms of Action

Both the mRNA-1273 (hereafter, 'Moderna') and BNT162b2 (hereafter, 'Pfizer-BioNTech') vaccines utilize a novel lipid nanoparticle-encapsulated mRNA which encodes for the spike protein, locking it into a three-dimensional shape that binds to human ACE-2 receptors. These receptors are on cells with which elicited virus-neutralizing antibodies must interact.[66] After cell fusion, the mRNA is inserted into the cytoplasm (and not the nucleus) of the cell. Molecular mechanisms read the vaccine mRNA and translate this into the spike protein, which can then be recognized by the immune system. As vaccinated cells die, spike proteins and protein fragments are recognized by antigen-presenting cells (major histocompatibility complex class II molecules), which then activate both T-helper (CD4) cells and T-cytotoxic (CD8) cells. Circulating B-cells attached to spike proteins are activated by CD4 cells, causing them to differentiate into plasma cells. Plasma cells then begin to produce huge amounts of antibodies against the viral spike proteins, and these antibodies are capable of neutralizing or destroying the virus. Any residual vaccine mRNA is destroyed by the cells.[67,68]

DNA vector vaccines also encode for the SARS-CoV-2 spike protein. The Ad26.COV2.S (hereafter, 'J&J/Janssen') vaccine uses an adenovirus vector (which has been genetically altered in the laboratory so that it cannot cause infection in humans) to carry genetic information for the

SARS-CoV-2 spike protein within the DNA of the adenovirus. None of the adenovirus DNA (which includes the genetically modified portion encoding for the spike protein) gets incorporated into human cellular DNA; rather, human host enzymes are used to convert the vaccine DNA into mRNA (and the remaining DNA is destroyed by the cell). Once the mRNA has been created by the cell, the mRNA migrates back into the cytoplasm of the host cell and the remainder of the immune system response is then identical to that which occurs following mRNA vaccine receipt.[68]

Vaccine Efficacy and Effectiveness

To date, studies of vaccine immunogenicity, efficacy and safety have predominantly been carried out in adults. Early studies of the Pfizer-BioNTech COVID-19 vaccine in adults found that the vaccine's efficacy in preventing symptomatic, laboratory-confirmed COVID-19 in persons without a history of previous COVID-19 was 91.1%.[69] A more recent meta-analysis published in September 2021 estimated the pooled effectiveness of the Pfizer-BioNTech vaccine to be 92.4% in preventing symptomatic laboratory-confirmed COVID-19, 94.3% effective in preventing COVID-19-related hospitalizations, 96.1% protective against COVID-19-related deaths, and 89.3% effective in preventing asymptomatic SARS-CoV-2 infection.[70] However, one should note that most of the data collection and analysis occurred prior to widespread circulation of the Delta and Omicron variants.

In the phase III clinical trial of the Moderna vaccine, the two-dose vaccine series exhibited 94.1% efficacy at preventing COVID-19 illness, including severe disease, in participants (all of whom were 18 years of age or older) at least 14 days after the second injection.[71] In the phase III trial of the J&J/Janssen vaccine in subjects $\geq$ 18 years, a single dose of vaccine protected against symptomatic disease and asymptomatic infection at least 14 days

after administration (vaccine efficacy, 66.9%; adjusted 95% confidence interval [CI], 59.0 to 73.4).[72]

With the emergence of SARS-CoV-2 variants and with potential waning of vaccine-induced population immunity,[73-75] it is currently unknown as to the precise duration of protective immunity afforded by vaccination against SARS-CoV-2. However, studies in different settings and countries have documented rates of COVID-19 cases and severe disease that are substantially higher in persons not fully vaccinated when compared to those in fully vaccinated persons. Individual symptoms of COVID-19 appear less commonly among vaccinated persons, and vaccinated persons infected with SARS-CoV-2 are more likely to be asymptomatic than unvaccinated individuals.[76] Evaluations of persons vaccinated months previously continue to demonstrate that vaccination is highly effective in preventing COVID-19.[77] In an analysis of COVID-19 cases among vaccinated persons aged $\geq$ 18 years across 13 US jurisdictions that linked case surveillance and immunization registry data, the rates of COVID-19 cases, hospitalizations, and deaths were substantially higher in unvaccinated persons compared with those in fully vaccinated individuals.[78] While this analysis revealed some decrease (~13%) in vaccination effectiveness against confirmed infection caused by the Delta variant relative to estimates reported before Delta's emergence, no appreciable declines in effectiveness against hospitalization or death were found.

The clinical trial of the Pfizer-BioNTech vaccine in children aged 5-11 years had far fewer participants than those of the adult COVID-19 vaccine trials and was originally limited to 2,268 children (though later as per the FDA's request an additional 1,591 vaccinated children were followed up for 2.5 weeks after their second dose to expand surveillance for adverse events). Phase I of the trial determined that two doses of a 10 μg vaccine dosing strength

administered 21 days apart were immunogenic, and that this lower dosing strength (relative to the 30 μg dosing strength administered to individuals ≥12 years) was the least reactogenic.[65,79] Pediatric primary care providers who administer Pfizer-BioNTech vaccines to children between 5-11 years and to children ≥ 12 years should take special care to note that the 10 μg formulation for those 5-11 years has an orange vial cap, while the 30 μg formulation for those ≥ 12 years has a purple or gray vial cap (Table 2). Phases II and III of the trial identified a vaccine efficacy rate of 91% against symptomatic COVID-19.[79] Robust virus neutralization responses were observed in subjects one month after receiving the second dose of the vaccine series, and the observed responses were similar to those seen in immunized individuals between the ages of 16 - 25 years. Of note, immunogenicity of the Pfizer-BioNTech vaccine series in 12-to-15-year-olds had also been determined via comparing virus neutralization responses in that age group with those of immunized 16-to-25-year-olds (a process known as 'immunobridging').[80] The trial reported no cases of severe COVID-19, hospitalization, or death. Of the children who developed COVID-19, symptoms were milder in vaccine recipients, underscoring the vaccine protection conferred.[79,80]

Vaccination Recommendations for Children and Adolescents

The two-dose Pfizer-BioNTech primary series is currently the only FDA-approved or FDA-authorized vaccine for children and adolescents aged 5–17 years (Table 2). COVID-19 primary vaccination is recommended regardless of a history of underlying medical conditions, previous symptomatic or asymptomatic SARS-CoV-2 infection, or prolonged post-COVID-19 symptoms (Table 2). Immunocompromised individuals may not mount a protective immune response after initial vaccination. Additionally, their protection after primary vaccination appears to wane over time (thus making them again susceptible to severe COVID-19 disease). Such persons aged ≥ 12 years for Pfizer-BioNTech recipients (or alternatively ≥ 18 years for Moderna

recipients) should receive an additional primary dose of the same mRNA COVID-19 vaccine administered for the primary series ≥ 28 days after completion of the initial two-dose series. A booster dose of the Pfizer-BioNTech vaccine is permitted for adolescents 16-17 years of age who have completed their initial 2-dose series ≥ 6 months prior to provide additional protection (Table 2).

Pregnancy, Lactation, and Vaccination

COVID-19 vaccination is recommended for all pregnant and lactating women. Pregnant and recently pregnant people (for at least 42 days following the end of pregnancy) with COVID-19 are at increased risk for severe illness compared to non-pregnant people. Infected women are at increased risk for preterm birth and might be at increased risk for other adverse pregnancy complications and outcomes such as preeclampsia, coagulopathy, and stillbirth. Maternal infection may result in the admission of her COVID-19-infected newborn to a neonatal intensive care unit. None of the currently FDA-approved or FDA-authorized COVID-19 vaccines contain live attenuated SARS-CoV-2 antigen, and none cause COVID-19 infection in either the pregnant or lactating women or the fetuses. A conversation between the patient and her providers may assist with decisions about the use of a COVID-19 vaccine; however, approval by a healthcare professional is not required before vaccination.

Adverse Reactions Following Vaccination

Adult and adolescent COVID-19 vaccine recipients have reported local and systemic reactions that were temporary and mostly of a mild-to-moderate intensity. These side effects have been similar to those seen with other routinely administered vaccines and include soreness and/or redness at the injection site, fatigue, fever, chills, headache, myalgias, and arthralgias. For some individuals, these side effects may be more pronounced after the second dose of a two-dose

series. Anaphylaxis has been observed following receipt of COVID-19 mRNA vaccines, but this has been rare (approximately 2 to 5 people per million vaccinated in the United States**)**. In a review of Pfizer-BioNTech vaccine safety among adolescents, the CDC (using data from the Vaccine Adverse Event Reporting System [VAERS] and the smartphone-based active surveillance system [v-safe]) noted that reactions, except for myocarditis, either did not interfere with normal activities or had mild interference with these activities.[81] Reports of death after COVID-19 vaccination are extremely rare**.**

Cases of myocarditis and myopericarditis (hereafter, 'myocarditis') have been reported following mRNA COVID-19 vaccination (Pfizer-BioNTech and Moderna), particularly in adolescents and young adults.[82] There does appear to be a slightly increased risk of myocarditis development after receipt of an mRNA COVID-19 vaccine. Among people ≥ 12 years, cases have occurred predominantly in males aged 12-29 years, and typically within the first week after receipt of the second dose of vaccine. Most affected patients have been hospitalized for brief periods of time. The majority achieved prompt resolution of acute symptoms and responded well to medications and rest. In one study among males aged 12-29 years, there were an estimated 39 to 47 cases of myocarditis for every million second doses of vaccine administered.[83]

Vaccine adverse reactions in children 5-11 years enrolled in the Pfizer-BioNTech trial were similar to those reported among older children and adults in frequency and severity, including pain at the injection site (71%), fatigue (39.4%), and headache (28%).[65,80] No cases of myocarditis were observed in trial subjects, though the trial was not large enough to assess rare adverse events. The risk of cardiac events in fully vaccinated teenaged individuals has been estimated to be 180 cases per 1 million males 12 to 15 years of age and 200 cases per 1 million for males 16 to 17 years of age.[65] Placing these estimates within the context of enrolling subjects

in a vaccine clinical trial, a clinical trial with 10,000 vaccinated subjects ages 5-11 years (i.e., 20,000 total study subjects when accounting for a placebo group) would have identified 1-2 cases of myocarditis.

The CDC continues to monitor vaccine safety in children through multiple mechanisms, including VAERS and the Vaccine Safety Datalink. When reviewing possible adverse events associated with mRNA vaccine receipt, pediatric primary care providers should emphasize to parents that the potential for development of myocarditis with COVID-19 infection is significantly higher than the risk of myocarditis occurrence following vaccine receipt. Among 36 million persons in the United States with health care encounters from March 2020 through February 2021, 0.01% had myocarditis. Across all ages, the risk of myocarditis was found to be almost 16 times higher for people with COVID-19 compared to those who were not infected. Among children, the myocarditis risk was 37 times higher for infected children under 16 years and seven times higher for infected people ages 16-39 years compared to their uninfected peers.[84] As the potential risk of complications stemming from pediatric COVID-19 infection (e.g., myocarditis, secondary bacterial infections, MIS-C, etc.) far outweighs the potential risk of vaccination-associated myocarditis, mRNA vaccine usage remains warranted for children and adolescents.

Vaccine Contraindications and Precautions[85]

The following are contraindications to vaccination with the Pfizer-BioNTech and Moderna vaccines:

- Severe allergic reaction after a previous dose of an mRNA COVID-19 vaccine or any of its components (including polyethylene glycol [PEG]). Severe allergic reactions include: a) anaphylaxis (that occurs within four hours of vaccine administration), b) angioedema

affecting the airway (i.e., the tongue, uvula or larynx, and c) diffuse rash which also involves mucosal surfaces (e.g., Stevens-Johnson Syndrome).

The following are precautions to vaccination with the Pfizer-BioNTech and Moderna vaccines:

- People who had an immediate (onset < 4 hours after vaccination), but non-severe, allergic reaction after a dose of one type of COVID-19 vaccine are considered to have a precaution for receipt of a subsequent dose of the same vaccine type. Non-severe allergic reactions include urticaria beyond the injection site and angioedema (visible swelling) involving the lips, facial skin, or skin in other locations. Referral to an allergist-immunologist may be considered for these individuals. Administering another vaccine type is also an option for those eligible to receive another vaccine type.
- People with a history of an immediate allergic reaction of any severity to a non-COVID-19 vaccine that contains multiple components (one or more of which is a component of an mRNA COVID-19 vaccine) and for whom it is unknown which component elicited the allergic reaction have a precaution to vaccination. These individuals may benefit from consultation with an allergist-immunologist.
- People with a contraindication to the J&J/Janssen vaccine have a precaution to mRNA vaccine receipt. Polysorbate is an ingredient in the J&J/Janssen vaccine. PEG and polysorbate are structurally related, and cross-reactive hypersensitivity between these compounds may occur. Patients with this precaution should undergo vaccination only in an appropriate setting under the supervision of a healthcare professional experienced in the management of severe allergic reactions.

The following are contraindications to vaccination with the J&J/Janssen vaccine:

- Severe allergic reaction after a previous dose of J&J/Janssen vaccine or any of its components (including polysorbate), with severe allergic reaction defined as noted above.

The precautions as noted above for mRNA vaccination also apply to the J&J/Janssen vaccine. Included in these precautions are people for whom mRNA vaccination is contraindicated due to a known allergy to PEG, and people for whom a second dose of mRNA vaccine is contraindicated. People with these precautions should undergo J&J/Janssen vaccination only in an appropriate setting under the supervision of a healthcare professional experienced in the management of severe allergic reactions.

Regardless of the type of COVID-19 vaccine received, all patients should be monitored for at least 15 minutes following vaccine administration. Individuals with a history of anaphylaxis due to any cause should be monitored for at least 30 minutes following vaccine administration.

Advocacy

Vaccine Advocacy

Primary care pediatricians are uniquely positioned to act as vaccine advocates and to address vaccine questions and hesitancy, as doing so has long been an integral aspect of well-child care. Indeed, assessing the COVID-19 vaccination status of all age-eligible household members is an important responsibility, as "cocooning" can protect children not yet age-eligible for COVID-19 vaccination. The AAP encourages pediatricians to offer COVID-19 vaccinations to eligible patients and their family members or at least be able to readily provide information on where to obtain a vaccine locally.[86] As calls to fight disinformation have been made, social media has become an increasingly valuable tool to counter and rebut misinformation about the

COVID-19 vaccine in pediatrics in order to reassure families that the pediatric medical community strongly encourages universal vaccination for those who are age-eligible.[87]

During the pandemic, pediatric primary care providers have been champions of public health measures promoting the vital importance of universal masking in school, as well as vaccination of eligible populations. Pediatric primary care providers are a trusted vaccine information source for parents,[88] and advocacy for vaccination of eligible pediatric populations has been and continues to be an essential responsibility for pediatricians.

Community Advocacy

Primary care pediatricians serve as advocates, community leaders, and multidisciplinary collaborators, and these duties have been emphasized because of the COVID-19 pandemic.[89] Pediatric primary care providers play a vital role in coordination of community resources, collaboration with schools and childcare centers, and through communication with other medical providers in the community. The role of pediatrician advocacy has been highlighted in numerous communities throughout the United States where collaboration with data collection and sharing, testing, treatment, and policy have been prioritized.[90-92] Exemplar communities have established pediatric collaboratives, with subsequent creation of listservs, accumulation of robust data sets, and crafting of local protocols designed to help inform local best practices and ultimately aid school groups in decision-making regarding safe school protocols.[90] Pediatricians have established learning networks across sectors and have built community partnerships with infrastructure designed to outlast the COVID-19 pandemic and ideally address public health needs in the years to come.[92]

Conclusions

The challenges and opportunities of the COVID-19 pandemic have reshaped the landscape of pediatric primary care. As the pandemic continues to evolve, pediatricians must remain adaptive to rapidly changing information, receptive to the ongoing evolution of diagnostic and treatment modalities, and advocates to promote vaccination and fight disinformation for the betterment of their patients and communities.

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Conflicts of Interest

The authors have no conflicts of interest to disclose.

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Table 1. Populations Eligible to Receive COVID-19 Monoclonal Antibody Products

*Must be ≥ 12 years of age, weigh ≥ 40 kg, with a positive SARS-CoV-2 viral test result, within 10 days of symptom onset, and with ≥ 1 of the following:
Obesity or being overweight (for example, adults with BMI > 25 kg/m^2, or if age 12-17, have BMI > 85^{th} percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm)
Pregnancy
Chronic Kidney Disease
Diabetes
Immunosuppressive disease or immunosuppressive treatment
Cardiovascular disease (including congenital heart disease) or hypertension
Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis and pulmonary hypertension
Sickle cell disease
Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)
Having a medical-related technological dependence (for example, tracheostomy, gastrostomy,

or positive pressure ventilation (not related to COVID-19))

*The listed age and weight criteria are specific to casirivimab and imdevimab (REGEN-COV™, Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA) and sotrovimab (GlaxoSmithKline, PLC, London, UK). Bamlanivimab and etesevimab (Lilly USA, LLC, Indianapolis, IN, USA) also has FDA EUA for children from birth to age 12 years with the listed high-risk conditions, and age < 1 year is also listed as an additional high-risk criterion for receipt of bamlanivimab and etesevimab.

Table 2. Clinical Considerations for Use of COVID-19 Vaccines

Coadministration with other vaccines	COVID-19 vaccines and other vaccines may be administered on the same day, as well as any interval without respect to timing. When deciding to administer COVID-19 vaccine with other vaccines, providers should consider whether the patient is behind or at risk of becoming behind on recommended vaccines, their risk of acquiring vaccine-preventable diseases (e.g., during an outbreak), and the reactogenicity profile of the vaccines being administered. **If multiple vaccines are administered at a single visit, administer each injection in a different injection site.**
Persons with prior or current COVID-19	COVID-19 vaccines can be administered safely to persons with prior SARS-CoV-2 infection. Defer vaccination until the individual has recovered from the acute illness and criteria have been met for discontinuation of isolation
Vaccination of people with a history of multisystem inflammatory syndrome in children (MIS-C)	Children with MIS-C have antibodies to SARS-CoV-2. However, it is unknown if this correlates with protection against reinfection and for how long protective antibody levels persist. The benefits of COVID-19 vaccination for children and adolescents (i.e., a reduced risk of severe disease including potential recurrence of MIS-C after reinfection) may outweigh a theoretical risk of an MIS-like illness or the risks of myocarditis following COVID-19 vaccination for people who meet all of the following criteria: • Clinical recovery from MIS-C has been achieved, including return to normal cardiac function; • It has been ≥90 days since the diagnosis of MIS-C; • The individual resides in an area of high or substantial transmission of SARS-CoV-2 or otherwise has an increased risk for SARS-CoV-2 exposure and

	transmission; **AND** • Onset of MIS-C occurred before any COVID-19 vaccination. Clinical recovery, including return to normal cardiac function, is an important factor when considering COVID-19 vaccination.
Persons who received monoclonal antibodies or convalescent plasma for COVID-19	Passive antibody product used for post-exposure prophylaxis: defer vaccine for 30 days Passive antibody product used for COVID-19 treatment: defer vaccine for 90 days
Persons with a known SARS-CoV-2 exposure	Individuals in community or outpatient settings should defer vaccination until the quarantine period has ended. Residents in congregate settings may be vaccinated if they do not have symptoms consistent with COVID-19.
Persons with underlying conditions	May receive COVID-19 vaccine
Individuals with moderate to severe immune compromise	Moderately and severely immunocompromised people may not mount a protective immune response after initial vaccination. Protection after primary vaccination may wane over time making them susceptible to severe COVID-19. Such persons aged ≥12 years (Pfizer-BioNTech recipients) or ≥18 years (Moderna recipients) should receive an additional primary dose of the same mRNA COVID-19 vaccine administered for the primary series. • 2-doses of an mRNA vaccine; administer an additional COVID-19 vaccine at least 28 days after completion of the initial 2-dose series. • J & J/Janssen COVID-19 vaccine; currently no recommendation for an additional dose. **Vaccinated immunocompromised individuals should continue to follow additional multilayered preventive measures.** As more data become available, this vaccine recommendation may be updated to include younger age groups.
Interchangeability of COVID-19 vaccine products	Any currently FDA-approved or FDA-authorized COVID-19 vaccine can be used when indicated. The CDC does not state a product preference. In general, primary series and additional primary doses should be with the same vaccine product. However, the use of heterologous booster doses is authorized.
Persons with history of myocarditis or pericarditis	There are no data on the safety of administering a subsequent dose of any COVID-19 vaccine to people who have had myocarditis or pericarditis after a dose of an mRNA COVID-19 vaccine. It is unclear if these persons are at increased risk of further adverse cardiac effects following a subsequent dose of

	the vaccine**. Until additional safety data are available,** if myocarditis or pericarditis occurred after a dose of an mRNA COVID-19 vaccine**, one** should **not receive a subsequent dose of any COVID-19 vaccine.** • A subsequent dose, however, may be considered in certain circumstances (assess personal risk of severe COVID-19 and level of community transmission). • A person with a history of myocarditis or pericarditis unrelated to an mRNA vaccine may receive COVID-19 vaccine • Administer after the episode has completely resolved.
History of Guillain-Barré syndrome	Can receive any COVID-19 vaccine. However, discuss the availability of mRNA vaccines to offer protection against COVID-19.
Vaccination of children and adolescents	Children and adolescents aged 5–17 years should receive the age-appropriate formulation of a COVID-19 primary vaccine series. At this time, the 2-dose Pfizer-BioNTech primary series is the only FDA-approved or FDA-authorized vaccine for persons aged 5–17 years. Vaccination is recommended for everyone aged ≥5 years, regardless of a history of underlying medical conditions, previous symptomatic or asymptomatic SARS-CoV-2 infection, or seropositivity. **Children should receive the age-appropriate COVID-19 vaccine formulation regardless of their size or weight.** Children aged 5–11 years should receive the 10 µg Pfizer-BioNTech vaccine (orange cap) formulation and adolescents aged ≥12 years should receive the 30 µg Pfizer-BioNTech vaccine (purple or gray cap) formulation. Vaccine dosages (for COVID-19 vaccines and for other routinely recommended vaccines) are based on age and not size or weight. Vaccine recommendations for young children may be updated as more data become available.
Booster dose	All persons aged ≥18 years of age **should receive** a booster dose of COVID-19 vaccine, even if they were <18 years of age at the time of the primary series. Persons who are 16 or 17 years old may receive a booster dose. Currently, CDC does not recommend a booster dose in children aged 5–15 years, regardless of other characteristics or medical conditions. Booster dose recommendations may be updated as more data from studies on long term protection become available. • People ≥18 years of age who received an mRNA primary series should receive a single COVID-19 vaccine booster dose at least 6 months after completion

	of the primary series. • Presently, only the Pfizer-BioNTech COVID-19 vaccine can be used for booster vaccination for those aged 16-17 years at least 6 months after completion of the primary series, and use should be based on their individual benefits and risks. • See CDC guidance for boosting with heterologous vaccines.

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